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Comparing Biomarker Profiles of Patients with Heart Failure: Atrial Fibrillation versus Sinus Rhythm and Reduced versus Preserved Ejection Fraction

Brief title: Atrial Fibrillation in Heart Failure

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Abstract

Aims: The clinical correlates and consequences of atrial fibrillation (AF) might be different between heart failure with reduced versus preserved ejection fraction (HFrEF vs. HFpEF). Biomarkers may provide insights into underlying pathophysiological mechanisms of AF in these different HF phenotypes.

Methods and Results: We performed a retrospective analysis of the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF), which was an observational cohort. We studied 2152 patients with HFrEF (EF<40%), of which 1419 were in sinus rhythm (SR) and 733 had AF. Another 524 patients with HFpEF (EF ≥50%) were studied, of which 286 in SR and 238 with AF. For the comparison of biomarker profiles, 92 cardiovascular risk markers were measured (Proseek® Olink Cardiovascular III panel). The circulating risk marker pattern observed in HFrEF was different than the pattern in HFpEF: in HFrEF, AF was associated with higher levels of 77 of 92 (84%) risk markers compared to sinus rhythm (SR); whereas in HFpEF, many more markers were higher in SR than in AF. Over a median follow-up of 21 months, AF was associated with increased mortality risk (multivariable hazard ratio [HR] of 1.27; 95% confidence interval [CI] 1.09-1.48, p=0.002); there was no significant interaction between heart rhythm and EF group on outcome.

Conclusion: In patients with HFrEF, the presence of AF was associated with a homogeneously elevated cardiovascular risk marker profile. In contrast, in patients with HFpEF, the presence of AF was associated with a more scattered risk marker profile, suggesting differences in underlying pathophysiological mechanisms of AF in these HF phenotypes.

Key words: Atrial fibrillation; heart failure; preserved ejection fraction; biomarkers.

Clinical perspective

In patients with HFrEF, cardiovascular risk markers were homogeneously higher in AF patients compared to patients in SR. This was in contrast to patients with HFpEF, where the risk marker profile was more scattered. Even though these findings do not have direct clinical implications, these different risk marker profiles might suggest that AF has a different pathophysiological role in HFrEF than it has in HFpEF. A better understanding of this potential difference of AF in the two HF phenotypes should be further investigated, since this might also give insights into potential differences in (response to) treatment of AF in HFrEF versus HFpEF. Moreover, the differences in risk marker profiles could potentially be helpful in finding a biomarker (panel) that is more accurate in diagnosing HFpEF in patients with concomitant AF than currently recommended diagnostics that are not specific for AF nor HFpEF (a combination of signs and/or symptoms, elevated levels of NT-proBNP and structural or functional cardiac abnormalities assessed by echocardiography). Ideally, the biomarker pattern of patients with ‘pure’ AF (without HFpEF) should be compared to the markers of patients with HFpEF without AF, and those with both AF and HFpEF, in order to find a biomarker with a higher discriminative capacity than NT-proBNP has.

Abbreviations list

AF = atrial fibrillation

ECG = electrocardiogram

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

LVEF = left ventricular ejection fraction

QoL = quality of life

SR = sinus rhythm

Introduction

Atrial fibrillation (AF) and heart failure (HF) share common risk factors, predispose to each other, and together herald a worse prognosis than either condition alone.(1-3) The majority of our knowledge on the AF-HF relationship stems from series based on HF with reduced ejection fraction (HFrEF). However, HF with preserved ejection fraction (HFpEF) accounts for up to half of HF diagnoses, and AF has a high prevalence in both HFrEF and HFpEF.(4-6).

HFpEF is a more heterogeneous syndrome than HFrEF, with highly prevalent co-morbidities and a higher prevalence among elderly, obese, and women.(7) The diagnosis of HFpEF in the setting of AF is challenging because risk factors and symptoms overlap. Moreover, levels of biomarkers, such as circulating natriuretic peptides, are influenced by both AF and HF, which further complicates the diagnosis of HFpEF.(5,8) Therefore, in most current HF trials, separate cutoffs for these natriuretic peptides are used for patients in sinus rhythm (SR) and those in AF.(9) However, the specific cutoffs that are used are still arbitrary and widely debated.

Since distinct differences in pathophysiology are seen between HFrEF and HFpEF, with pronounced differences in age, sex, etiology and response to therapy, it is possible that AF also plays a different role and reflects different pathophysiological processes in these HF phenotypes.(10-12) Biomarkers might have the potential to help us understand these possible differences in the underlying pathophysiological role of AF. Therefore, we performed a post-hoc analysis of BIOSTAT-CHF to study biomarker profiles of patients in AF versus SR in both HFrEF and HFpEF.

Methods

Patient population and study design

We performed a retrospective analysis of The BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF), which was an observational study and has been previously published.(13,14) In brief, a total of 4254 patients with new-onset or worsening signs and/or symptoms of HF from eleven European countries were included in BIOSTAT-CHF. Patients had to have objective evidence of cardiac dysfunction documented either by left ventricular ejection fraction (LVEF) of ≤40%, or plasma concentrations of NT-proBNP >2,000pg/ml. We included patients with either SR or AF/atrial flutter at baseline for our analysis. Those with a pacemaker rhythm and unknown atrial rhythm (n=466), other rhythm (n=63) or unknown rhythm (n=111) were excluded. A flowchart of the selected patients is presented in *Supplementary Figure 1*. Patients were categorized into two groups based on LVEF assessed by transthoracic echocardiography: HFrEF (<40%) and HFpEF (≥50%). Patients with unknown LVEF were excluded (n=345). Patients with a LVEF between 40-49% (HF with mid-range EF) were excluded in order to make a greater distinction between the two HF phenotypes (n=593). Quality of life (QoL) was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ).(15) Higher scores indicated a better QoL. Primary outcome was time to all-cause mortality. The study complies with the Declaration of Helsinki, medical ethics committee of participating centers approved the study, and all patients provided written informed consent.

Definition of atrial fibrillation

A standard 12-lead electrocardiogram (ECG) was performed at baseline. Patients were classified into AF or SR according to their heart rhythm at time of blood collection, registered on the baseline ECG.

Biomarkers

The Olink Cardiovascular III panel was used to create the biomarker profiles in the two HF phenotypes. This panel comprises 92 cardiovascular disease-related biomarkers, which were selected based on literature searches, disease association in the Coremine database, and in collaboration with experts within the cardiovascular field. Measurement of these 92 biomarkers was performed by Olink

Bioscience analysis service (Uppsala, Sweden), using the Proseek® multiplex Inflammatory^{96*96} kit.(16) The Proseek® reagents are based on the Proximity Extension Assay (PEA) technology, which binds 92 oligonucleotide-labeled antibody probe pairs to the target biomarker. For further quantification, real-time PCR was performed. Olink wizard and GenEx software were used for further data analysis. Proseek® data are presented as arbitrary units (AU) on a Log2 scale. Every marker was categorized by current literature in one or more categories.(17) The abbreviations and full names of the 92 biomarkers and their categories are presented in *Supplementary Table 1*.

Statistical analyses

Normally distributed variables were depicted as means ± standard deviation, non-normally distributed variables as median with the first and third quartile (Q1-Q3), categorical variables as numbers with percentages. Means of continuous variables were compared by one-way analysis of variance (ANOVA) or Kruskal-Wallis test, while categorical variables were compared by the χ^2 test. Kaplan-Meier survival curves were compared using the log-rank statistic. Cox regression models were used to adjust for the effect of covariates and to calculate hazard ratios (HR). The Cox proportional hazards assumption was assessed by visually inspecting plots of Schoenfeld residuals against time, which showed proportionality in both the total cohort, as in the two HF subgroups (HFrEF and HFpEF) separately. The median level of each biomarker in the AF group was divided by the median level of this biomarker in the SR group to produce a ratio. This ratio (converted into a percentage) was visualized in figure 1, where every bar represents this difference (%), which can either be positive (higher level in AF) or negative (higher level in SR). Interaction testing was performed to determine whether the effect of heart rhythm differed between the HF phenotypes, with regard to outcome (interaction term in the cox regression model) and with regard to every separate biomarker (interaction term in the linear regression model). We also tested three falsification hypotheses to see whether other important covariates gave similar biomarker patterns in HFrEF and HFpEF as found for heart rhythm. Rejection of these hypotheses would strengthen the fact that the biomarker profiles found for AF versus SR were specific for heart rhythm, and not importantly influenced by other confounders. These three hypotheses were formulated for age (below versus above the mean age in HFrEF and HFpEF),

renal disease (above versus below an estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73m^2), and ischemic heart disease (previous myocardial infarction, percutaneous intervention and/or coronary artery bypass graft, 'yes' versus 'no'). A substantial number of the previously mentioned definitions and analyses were added or adjusted during the review process. Therefore, the findings should be considered exploratory. In general, a two-tailed p-value of <0.05 was considered statistically significant. In the tables where the associations of 92 biomarkers were tested, the p-values were controlled for the false discovery rate using the Benjamini-Hochberg method. For testing interactions, a p-value of <0.1 was considered significant.

Results

Patient characteristics

We studied a total of 2676 HF patients, of which 1703 were in SR (64%) and 971 had AF (36%). Baseline characteristics are presented in *Table 1*. These patients were further stratified in 2152 HFrEF patients, of which 1419 were in SR and 733 had AF, and 524 HFpEF patients, of which 286 were in SR and 238 had AF. The baseline characteristics of these 4 subgroups are presented in *Table 2.* In both HF phenotypes, patients with AF were significantly older than their counterparts in SR. Patients with AF and HFpEF were the oldest (79 ± 9 years) and patients in SR and HFrEF the youngest (69 ± 12 years). Men were more likely to have AF and HFrEF, whereas a similar number of men and women had AF and HFpEF. In both HFrEF and HFpEF, patients with AF less often had a history of coronary artery disease (HFrEF: 51% in SR vs. 43% in AF, p=0.001 and HFpEF: 54% in SR vs. 28% in AF, p<0.001). Patients with HFpEF reported the lowest QoL, where no differences were seen between patients with AF and SR. However, in HFrEF, AF patients reported significantly lower QoL *(Figure 2).*

Biomarker profiles

In HFrEF, the relative levels of 77 of 92 (84%) cardiovascular risk markers were higher in patients with AF than in those in SR, which resulted in a homogeneous risk marker pattern *(Figure 1).* This was in contrast to the pattern seen in HFpEF, where the risk marker profile of patients with AF versus

SR was much more scattered; 51 (55%) risk markers were higher in patients in SR and 36 (39%) in patients with AF *(Figure 1).* The median Log2 levels of the 92 biomarkers for SR and AF are presented in *Supplementary Table 2* for HFrEF and *Supplementary Table 3* for HFpEF. To find out whether these differences in biomarker profiles between HFrEF and HFpEF were importantly influenced by other covariates, interactions for every biomarker between rhythm group and HF phenotype were tested in a univariable and multivariable model. This resulted in a significant interaction between rhythm and HF phenotype in 44 biomarkers, of which 26 (59%) remained significant in the multivariable model *(Supplementary Table 4).*

Apart from the differences seen in overall risk marker pattern when comparing HFrEF and HFpEF, several similarities were found when studying the top five markers with the largest difference between AF and SR (being highest in AF). In both HFrEF and HFpEF, NT-proBNP was the risk marker with the largest difference between AF and SR. Beyond NT-proBNP, two other markers were found in this top five in both HFrEF and HFpEF: ST2 and SPON1. A sensitivity analysis revealed no notable differences between patients who had a history of AF versus patients with AF on the baseline ECG. The falsification hypotheses about age, renal disease and ischemic heart disease showed homogeneous patterns with the most elevated risk markers in the group at risk (older, eGFR <60 and ischemic heart disease) in both HFrEF and HFpEF (*Supplementary Figure 2*), in contrast to the findings with AF versus SR in HFrEF and HFpEF.

Outcome

The median follow-up duration was 21 months (IQR 11-32 months). AF was associated with increased mortality risk (HR 1.44; 95% confidence interval [95%CI] 1.25-1.66, p<0.001) in the total cohort *(Figure 3)* and in the HF phenotypes (HFrEF: HR 1.41; 95%CI 1.19-1.68, p<0.001 and HFpEF: HR 1.39; 95%CI 1.05-1.83, p=0.022) *(Figure 4).* After adjustment for covariates, the association of AF on outcome remained significant in the total cohort (HR 1.27; 95%CI 1.09-1.48, p=0.002), but no longer in HFpEF (*Table 3*). However, there was no significant interaction between heart rhythm and the HF phenotypes on outcome (p=0.71). Of the previously mentioned top five biomarkers, NT-proBNP, ST2 and SPON1 were all strongly associated with all-cause mortality for patients in SR and AF in both HFrEF and HFpEF *(Supplementary Table 5).*

Discussion

In this study, the presence of AF was associated with a homogeneously elevated cardiovascular risk marker profile in patients with HFrEF, whereas in HFpEF, the presence of AF was associated with a much more scattered risk marker profile. These findings suggest that there might be differences in underlying pathophysiological mechanisms of AF in these two HF phenotypes.

Patient characteristics

Patients with AF reported a significantly lower QoL than patients in SR in HFrEF, whereas QoL was not influenced by heart rhythm among patients with HFpEF. Interestingly, patients with HFpEF reported the lowest QoL. In our view, the overall lower QoL in our HFpEF patients could be explained by the higher age and higher number of women.(18) However, after adjustment for age and sex, AF still had a significantly negative influence on QoL in HFrEF but not in HFpEF. The levels of NT-proBNP of the patients with HFpEF were relatively high, also in the SR group, due to the natriuretic peptide entry criteria for patients with a LVEF>40% in BIOSTAT-CHF. This might reflect the inclusion of quite severe HFpEF in our cohort, which could have directly resulted in the lower QoL.

Similar to previous studies, our study found that men are more likely to have AF, especially in HFrEF.(19,20) In HFpEF, where more women were included, the prevalence of AF in men and women was similar. Furthermore, patients without a history of coronary artery disease were more likely to have AF, in accordance with previous studies.(20-23) Exact mechanisms of the difference between the sexes and associations with etiology are yet to be discovered.

Biomarker profiles

The biomarker profiles of patients with AF versus SR revealed prominent differences between HFrEF and HFpEF. The great majority of these markers were elevated in patients with AF in HFrEF. We hypothesize that AF is a reflection of a more advanced disease state in HFrEF, since almost all of these markers are associated with worse prognosis. In contrast, in HFpEF, the risk marker profile was more scattered, with less than half of the biomarkers being more elevated in the AF group. AF may be a separate bystander along with a high prevalence of other comorbidities in HFpEF, instead of a

marker for disease severity. Furthermore, it is possible that a higher number of patients had prior AF before HFpEF developed, which is shown to have a better prognosis as compared to patients who develop AF after HF.(24,25) Another possible explanation is the misclassification of HF in patients with AF. The challenges of making an accurate diagnosis of symptomatic AF (without HF) versus HFpEF with concomitant AF have been previously discussed.(5,9) It is plausible that patients with AF but without actual HFpEF were included in this group. Furthermore, since AF itself raises natriuretic peptides, the NT-proBNP inclusion criterion above >2,000pg/ml in BIOSTAT-CHF may have led to inclusion of patients in SR having more severe HFpEF. Greater severity of HF in patients with HFpEF and SR is supported by their low QoL, high mortality rates and higher numbers of elevated risk markers compared to those in SR and HFrEF.

Despite the differences between the biomarker profiles seen in the two HF phenotypes, several similarities were found. Three out of five markers with the largest differences between AF and SR patients were seen in both HFrEF and HFpEF. NT-proBNP, the marker with the largest difference between AF and SR in both HF phenotypes, is well known to be importantly influenced by AF. The other two markers in both HFrEF and HFpEF were ST2 and SPON1. Soluble ST2 is released from the myocardium and vascular endothelial cells in response to pressure and/or volume overload, which is seen in both HFrEF and HFpEF, and which is also more pronounced in patients with AF.(26) Spondin-1 (SPON1) has been less explored in the cardiovascular field, but associations of this marker have been identified with incident HF, worsened systolic function and hypertension.(27) No specific literature has been found about SPON1 in AF, but this biomarker has been related to angiogenesis and other prothrombotic markers, which perhaps could be linked to the mechanisms of thrombogenesis seen in AF.(17,28)

In HFrEF, the other two top five risk markers were neurogenic locus notch homolog protein 3 (NOTCH 3) and matrix metalloproteinase-2 (MMP2), which were both categorized as markers of remodeling. The two other markers that were most pronounced in patients with AF and HFpEF, were platelet-derived growth factor subunit-A (PDGFSUBUNITA) and insulin-like growth factor-binding protein-1 (IGFBP1), which are both not cardiac-specific markers, and both are linked to cellular growth factors.(29) No specific information is available about the biology and relation between AF

and these two markers. Our findings encourage additional studies investigating the underlying mechanisms and the clinical relevance of our findings.

Strengths

The novelty of this study is the measurement of 92 both established and novel cardiovascular risk markers, which resulted in the comparison of the biomarker profiles in HFrEF versus HFpEF. BIOSTAT-CHF is a reflection of real world contemporary European HF patients, due to the inclusion of patients from eleven European countries, aiming for optimal HF treatment. Furthermore, the HF phenotypes were defined according to the latest ESC guidelines EF cutoffs.(30)

Limitations

The results of the current study are based on *post hoc* analyses. The sample size of HFpEF was smaller than in HFrEF, which could explain the differences found in outcome between HFrEF and HFpEF after adjustment for covariates. However, since there was no significant interaction between heart rhythm and HF phenotype, it is unlikely that a larger sample size of HFpEF would have resulted in a contrasting outcome of AF-HFpEF patients. As discussed above, misclassification of AF versus HFpEF is possible, patients with more severe HFpEF in SR may have been included due to the natriuretic peptide inclusion criterion of BIOSTAT-CHF. This inclusion criterion could also have resulted in positive confounding with higher event rates in the HFpEF group, therefore we did not directly compare AF-HFrEF with AF-HFpEF. Unfortunately, we have no information about patients developing AF during follow-up. Furthermore, there is a lack of data on the type of AF (e.g. paroxysmal, persistent, permanent) and on applied therapies for AF. The questionnaire used for assessing QoL is not generally used in AF cohorts, which could have led to ignorance of AF specific symptoms that can influence QoL.

Conclusion

This study revealed that the presence of AF was associated with a homogeneously elevated cardiovascular risk marker profile in patients with HFrEF, whereas in HFpEF, the presence of AF was

associated with a more scattered risk marker profile. These findings suggest that there might be differences in underlying pathophysiological mechanisms of AF in these two HF phenotypes.

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Figure Legends

Figure 1: Graphical representation of the risk marker profile in patients with SR versus AF in HFrEF (left) and HFpEF (right). A blue bar indicates a higher level of this marker in patients with AF, whereas a red bar reflects a higher level in patients in SR. The top five biomarkers with the largest difference between SR and AF were highlighted in blue, with the percentage indicating the magnitude of this difference.
HFrEF=heart failure with reduced ejection fraction, HFpEF=heart failure with preserved ejection fraction, SR=sinus rhythm, AF=atrial fibrillation, MMP2=matrix metalloproteinase-2, NOTCH3=neurogenic locus notch homolog protein-3, NTPROBNP=N-terminal pro-B-type natriuretic peptide, SPON1=spondin-1, ST2=ST-2 protein, IGFBP1=insulin-like growth factor-binding protein-1, PDGFSUBUNITA=platelet-derived growth factor subunit-A.

Figure 2. Quality of Life; KCCQ scores for patients in SR versus AF

Figure 3. Kaplan-Meier analysis showing the survival of patients in SR versus AF

Figure 4. Kaplan-Meier analysis showing the effect of AF on survival by HF phenotype

Table 1. Baseline characteristics of heart failure patients in SR and AF

	Total cohort		
	Sinus rhythm n=1705 (64%)	Atrial fibrillation n=971 (36%)	p-value
Clinical			
Age (years)	70±12	75±10	**<0.001**
Women (%)	527 (31)	263 (27)	**0.041**
BMI (kg/m2)	28.0±5.9	28.6±5.9	**0.009**
NYHA (%)			**0.003**
1	122 (8)	43 (5)	
2	749 (48)	407 (45)	
3	570 (37)	363 (40)	
4	117 (8)	85 (10)	
LVEF, %	33±13	36±14	**<0.001**
Systolic blood pressure (mmHg)	126±22	124±21	0.161
Diastolic blood pressure (mmHg)	73±13	74±14	**0.001**
Heart rate (beats/minute)	76±18	90±26	**<0.001**
History of (%)			
Atrial fibrillation	273 (16)	864 (89)	**<0.001**
Coronary artery disease*	874 (52)	379 (39)	**<0.001**
Valvular surgery	87 (5)	96 (10)	**<0.001**
Stroke	182 (11)	131 (14)	**0.034**
Hypertension	1017 (60)	586 (60)	0.756
Diabetes Mellitus	541 (32)	306 (32)	0.962
COPD	305 (18)	170 (18)	0.837
Renal disease	482 (29)	357 (37)	**<0.001**
Physical examination (%)			
Rales	789 (48)	519 (55)	**<0.001**
Edema	768 (54)	591 (69)	**<0.001**
JVP	323 (26)	286 (40)	**<0.001**
Hepatomegaly	141 (9)	131 (14)	**<0.001**
KCCQ			
Functional status score	52 [32-75]	45 [27-64]	**<0.001**
Clinical summary score	49 [30-71]	42 [24-61]	**<0.001**
Overall score	50 [32-70]	43 [27-60]	**<0.001**
Laboratory data			
NT-proBNP (ng/L)	2030 [613-5797]	3093 [1548-6287]	**<0.001**
Creatinine (µmol/L)	97 [80-119]	101 [84-127]	**<0.001**
TSH (mU/L)	1.8 [1.0-2.7]	1.9 [1.2-3.1]	**0.025**
fT4 (pmol/L)	15.3 [13.2-17.9]	15.7 [13.9-18.2]	**0.018**
Medications (%)			
ACE/ARB	1267 (74)	658 (68)	**<0.001**
β-Blocker	1348 (79)	760 (78)	0.665
MRA	792 (47)	428 (44)	0.252
Diuretics	1701 (100)	961 (99)	**0.014**

*Coronary artery disease: previous myocardial infarction, percutaneous coronary intervention and/or coronary artery bypass graft. BMI=body mass index, NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, COPD=chronic

obstructive pulmonary disease, JVP=jugular venous pressure, KCCQ=Kansas City Cardiomyopathy Questionnaire, NT-proBNP=N-terminal pro-B-type natriuretic peptide, TSH=thyroid stimulating hormone, fT4=free thyroxine, ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, MRA=mineralocorticoid receptor antagonist.

Table 2. Baseline characteristics by HF phenotype comparing patients in SR and AF

	HFrEF			HFpEF		
	SR n=1419 (66%)	AF n=733 (34%)	p-value	SR n=286 (55%)	AF n=238 (45%)	p-value
Clinical						
Age (years)	69±12	74±10	**<0.001**	75±10	79±9	**<0.001**
Women (%)	390 (27)	152 (21)	**0.001**	137 (48)	111 (47)	0.841
BMI (kg/m2)	27.7±5.6	28.4±5.6	**0.015**	29.4±6.9	29.5±6.8	0.861
NYHA (%)			**0.005**			0.796
1	115 (9)	35 (5)		7 (3)	8 (4)	
2	650 (51)	325 (48)		99 (36)	82 (36)	
3	444 (35)	268 (40)		126 (46)	95 (42)	
4	73 (6)	45 (7)		44 (16)	40 (18)	
LVEF, %	28±7	28±7	0.115	58 ± 6	58±7	0.857
Systolic blood pressure (mmHg)	124±22	123±21	0.318	133 ± 25	128±21	**0.024**
Diastolic blood pressure (mmHg)	74±13	76±13	**0.001**	67 ± 13	71±15	**0.004**
Heart rate (beats/min)	77±18	91±25	**<0.001**	73 ± 17	88±27	**<0.001**
History of (%)						
Atrial fibrillation	227 (16)	653 (89)	**<0.001**	46 (16)	211 (89)	**<0.001**
Coronary artery disease*	720 (51)	314 (43)	**0.001**	154 (54)	65 (28)	**<0.001**
Valvular surgery	61 (4)	72 (10)	**<0.001**	26 (9)	24 (10)	0.813
Stroke	132 (9)	93 (13)	**0.019**	50 (18)	38 (16)	0.746
Hypertension	814 (57)	428 (59)	0.682	203 (71)	158 (66)	0.300
Diabetes Mellitus	443 (31)	221 (30)	0.646	98 (34)	85 (36)	0.767
COPD	230 (16)	121 (17)	0.908	75 (26)	49 (21)	0.153
Renal disease	355 (25)	250 (34)	**<0.001**	127 (46)	107 (46)	1.000
Physical examination (%)						
Rales	647 (47)	368 (52)	**0.032**	142 (51)	151 (65)	**0.003**
Edema	596 (50)	428 (67)	**<0.001**	172 (68)	163 (74)	0.196

JVP	256 (25)	204 (39)	**<0.001**	67 (31)	82 (42)	**0.025**
Hepatomegaly	131 (9)	113 (16)	**<0.001**	10 (4)	18 (8)	0.089
KCCQ						
Functional status score	55 [36-75]	46 [27-66]	**<0.001**	39 [23-63]	38 [21-58]	0.530
Clinical summary score	51 [32-73]	44 [26-63]	**<0.001**	39 [20-60]	37 [23-56]	0.691
Overall score	52 [35-71]	45 [29-63]	**<0.001**	42 [25-59]	39 [25-53]	0.365
Laboratory data						
NT-proBNP (ng/L)	2642 [855-6725]	3573 [1853-7127]	**<0.001**	802 [261-3092]	2359 [1136-4799]	**<0.001**
Creatinine (µmol/L)	97 [80-118]	104 [87-130]	**<0.001**	95 [74-124]	95 [78-122]	0.751
TSH (mU/L)	1.8 [1.1-2.8]	1.9 [1.3-3.2]	**0.009**	1.6 [1.0-2.6]	1.8 [0.9-2.9]	0.695
fT4 (pmol/L)	15.1 [13.0-17.8]	15.5 [13.7-18.0]	0.055	15.7 [13.8-18.0]	16.0 [14.1-18.6]	0.328
Medications (%)						
ACE/ARB	1079 (76)	532 (73)	0.089	188 (66)	126 (53)	**0.004**
β-Blocker	1168 (82)	607 (83)	0.819	180 (63)	153 (64)	0.819
MRA	738 (52)	365 (50)	0.353	54 (19)	63 (27)	**0.049**
Diuretics	1416 (100)	729 (100)	0.373	285 (100)	232 (98)	0.076

* Coronary artery disease: previous myocardial infarction, percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG).

HFrEF=heart failure with reduced ejection fraction, HFpEF=heart failure with preserved ejection fraction, BMI=body mass index, NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, COPD=chronic obstructive pulmonary disease, JVP=jugular venous pressure, KCCQ=Kansas City Cardiomyopathy Questionnaire, NT-proBNP=N-terminal pro-B-type natriuretic peptide, TSH=thyroid stimulating hormone, fT4=free thyroxine, ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, MRA=mineralocorticoid receptor antagonist.

Table 3. Multivariable cox regression analysis for all-cause mortality by HF phenotype

	Univariable analysis		Multivariable analysis*		Multivariable analysis**	
	HR (95% CI), AF vs. SR	p-value	HR (95% CI), AF vs. SR	p-value	HR (95% CI), AF vs. SR	p-value
HFrEF	1.41 (1.19-1.68)	**<0.001**	1.24 (1.04-1.47)	**0.015**	1.28 (1.07-1.53)	**0.007**
HFpEF	1.39 (1.05-1.83)	**0.022**	1.11 (0.83-1.48)	0.480	1.10 (0.81-1.49)	0.550
Overall	1.44 (1.25-1.66)	**<0.001**	1.22 (1.05-1.41)	**0.009**	1.27 (1.09-1.48)	**0.002**
					P-value for interaction: 0.71	

*Adjusted for age

**Adjusted for age, sex, body mass index, previous myocardial infarction/percutaneous intervention and/or coronary artery bypass graft, hypertension and renal disease.

HR=hazard ratio, CI=confidence interval, AF=atrial fibrillation, SR=sinus rhythm, HFrEF=heart failure with reduced ejection fraction, HFpEF=heart failure with preserved ejection fraction.

Figure 1.

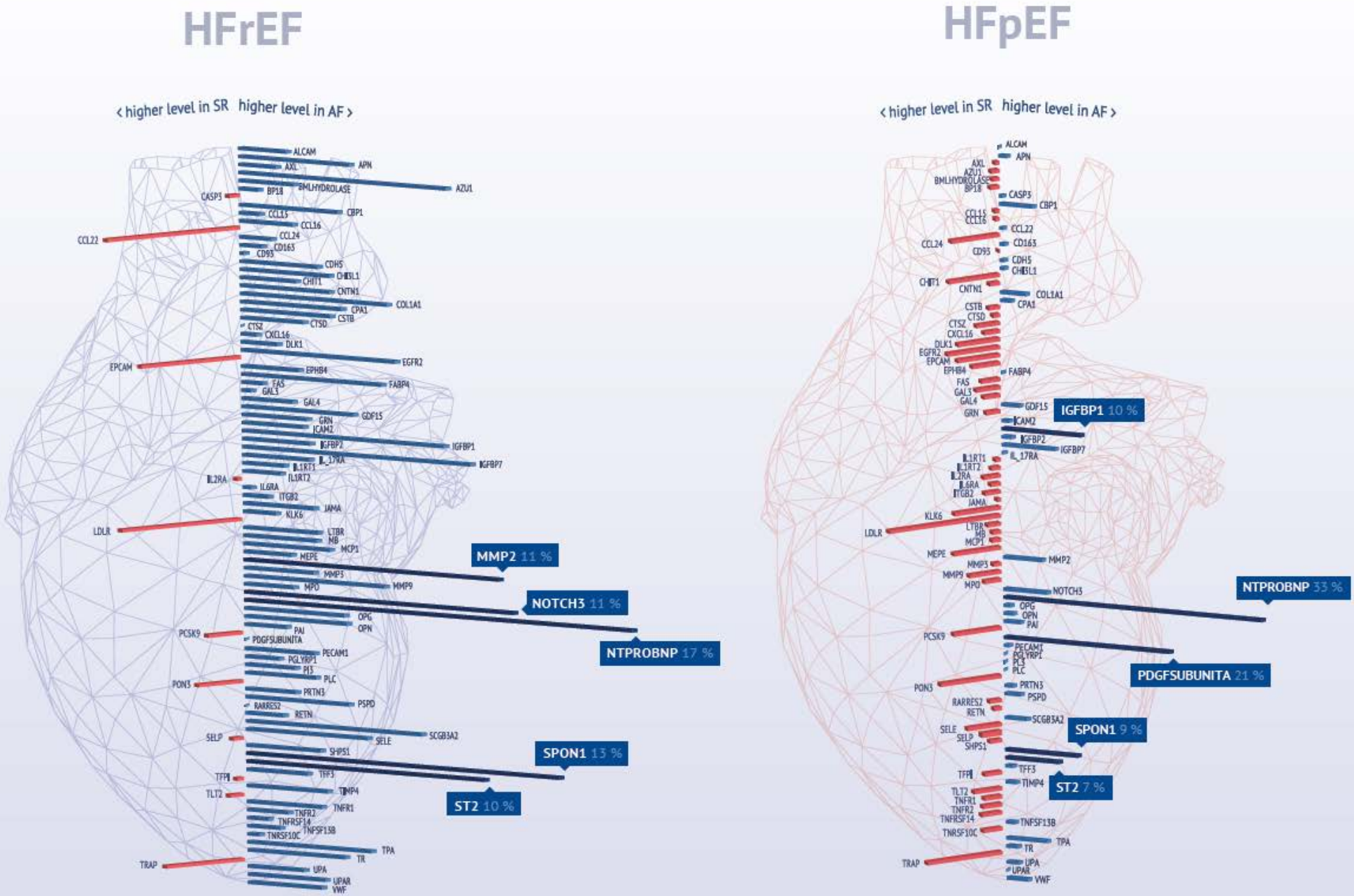

HFrEF
‹ higher level in SR higher level in AF ›
ALCAM
APN
AXL
AZU1
BMLHYDROLASE
BP18
CASP3
CBP1
CCL15
CCL16
CCL22
CCL24
CD163
CD93
CDH5
CHI3L1
CHIT1
CNTN1
COL1A1
CPA1
CSTB
CTSD
CTSZ
CXCL16
DLK1
EGFR2
EPCAM
EPHB4
FABP4
FAS
GAL3
GAL4
GDF15
GRN
ICAM2
IGFBP1
IGFBP2
IGFBP7
IL_17RA
IL1RT1
IL1RT2
IL2RA
IL6RA
ITGB2
JAMA
KLK6
LDLR
LTBR
MB
MCP1
MEPE
MMP2
MMP3
MMP9
MPO
NOTCH3
OPG
OPN
PAI
PCSK9
PDGFSUBUNITA
PECAM1
PGLYRP1
PI3
PLC
PON3
PRTN3
PSPD
RARRES2
RETN
SCGB3A2
SELE
SELP
SHPS1
SPON1
TFF3
TFPI
TIMP4
TLT2
TNFR1
TNFR2
TNFRSF14
TNFSF13B
TNRSF10C
TPA
TR
TRAP
UPA
UPAR
VWF
MMP2 11 %
NOTCH3 11 %
NTPROBNP 17 %
SPON1 13 %
ST2 10 %
HFpEF
‹ higher level in SR higher level in AF ›
IGFBP1 10 %
NTPROBNP 33 %
PDGFSUBUNITA 21 %
SPON1 9 %
ST2 7 %

Figure 2.

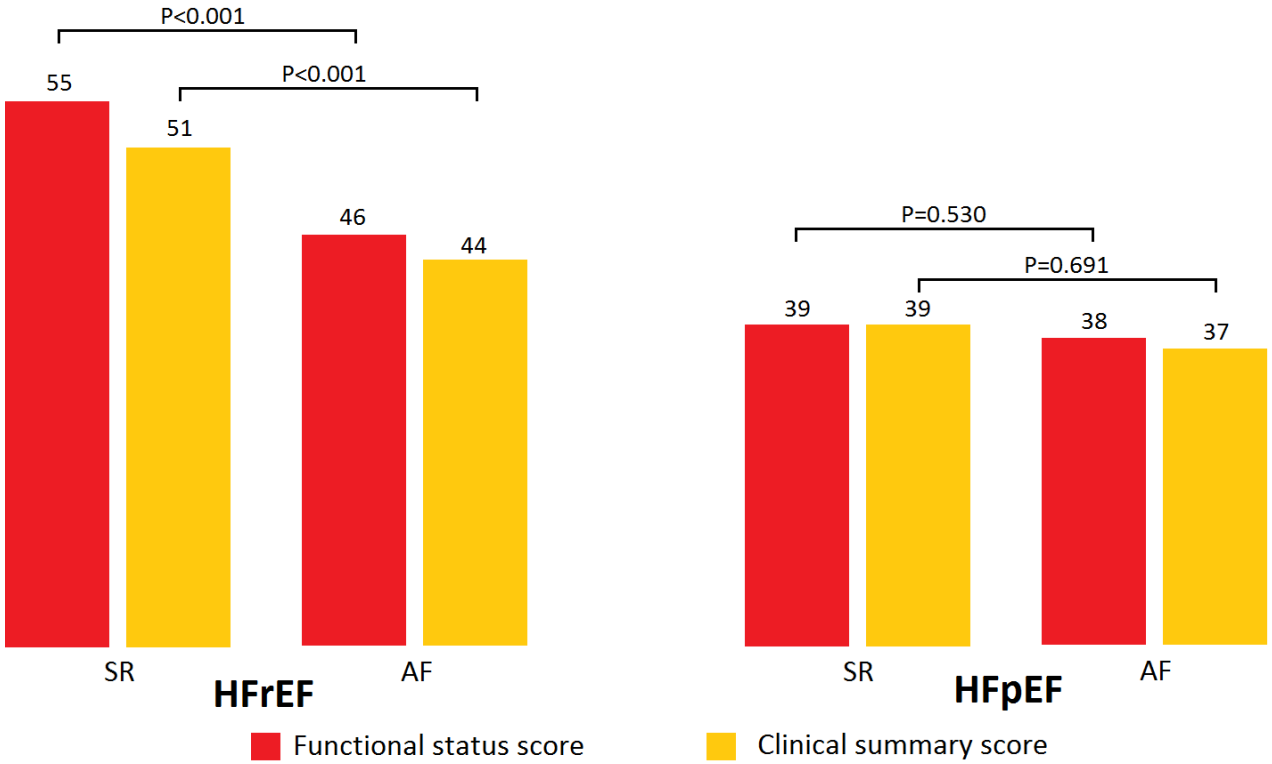

P<0.001
P<0.001
55
51
46
44
SR
AF
HFrEF
P=0.530
P=0.691
39
39
38
37
SR
AF
HFpEF
Functional status score
Clinical summary score

Figure 3.

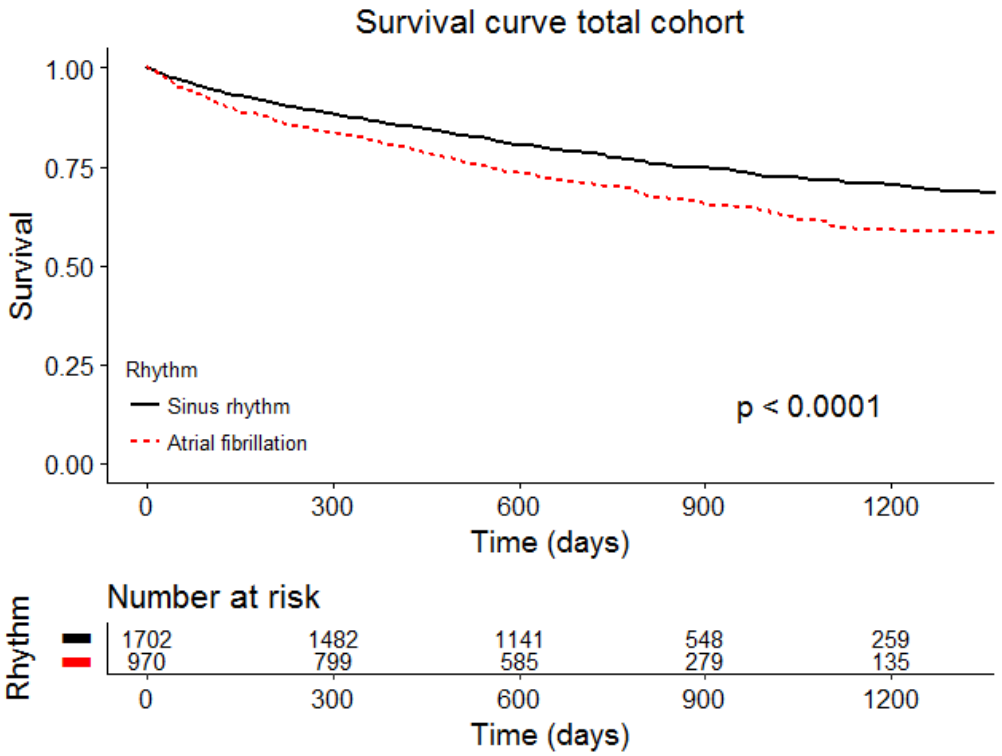
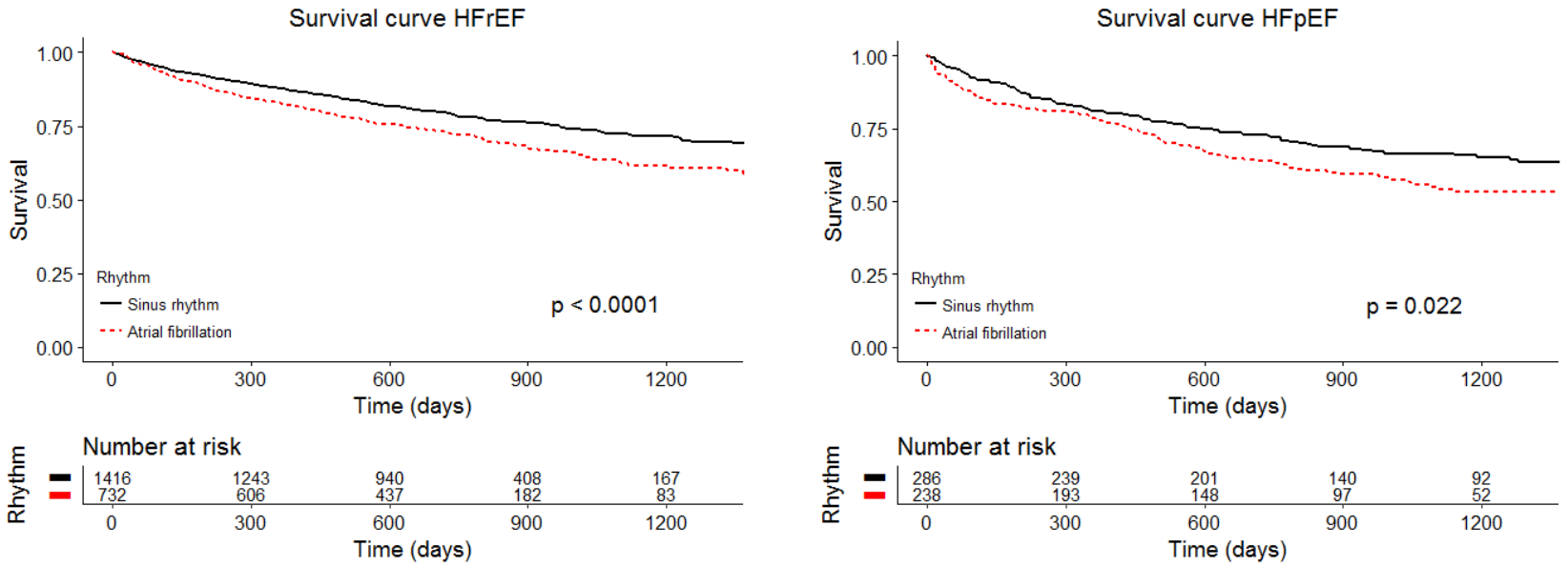
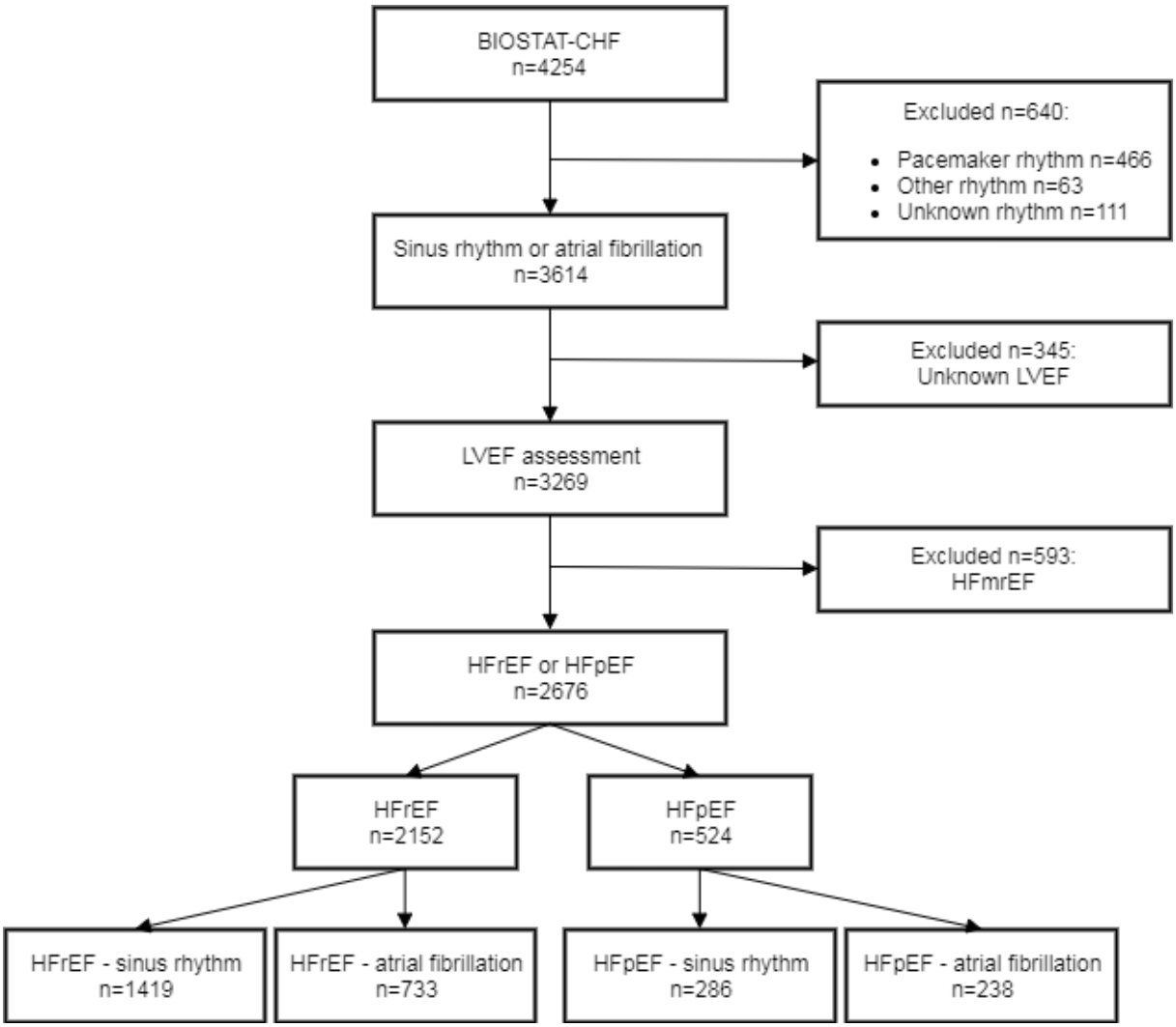

Survival curve total cohort
1.00
0.75
0.50
0.25
0.00
Survival
Rhythm
Sinus rhythm
Atrial fibrillation
p < 0.0001
0
300
600
900
1200
Time (days)
Number at risk
Rhythm
1702
970
1482
799
1141
585
548
279
259
135
0
300
600
900
1200
Time (days)

Figure 4.

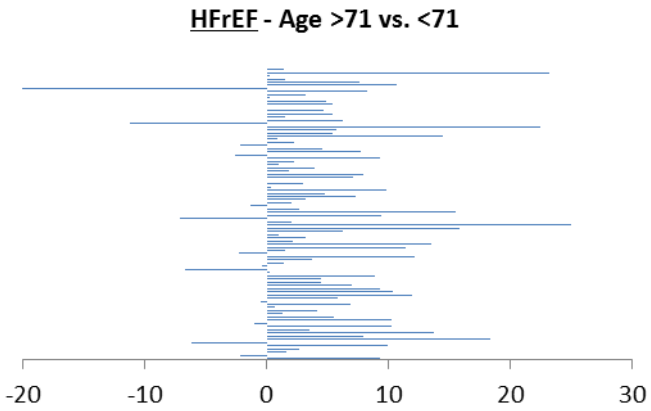

Survival curve HFrEF
Survival
1.00
0.75
0.50
0.25
0.00
Rhythm
Sinus rhythm
Atrial fibrillation
p < 0.0001
0
300
600
900
1200
Time (days)
Number at risk
Rhythm
1416
732
1243
606
940
437
408
182
167
83
0
300
600
900
1200
Time (days)
Survival curve HFpEF
Survival
1.00
0.75
0.50
0.25
0.00
Rhythm
Sinus rhythm
Atrial fibrillation
p = 0.022
0
300
600
900
1200
Time (days)
Number at risk
Rhythm
286
238
239
193
201
148
140
97
92
52
0
300
600
900
1200
Time (days)

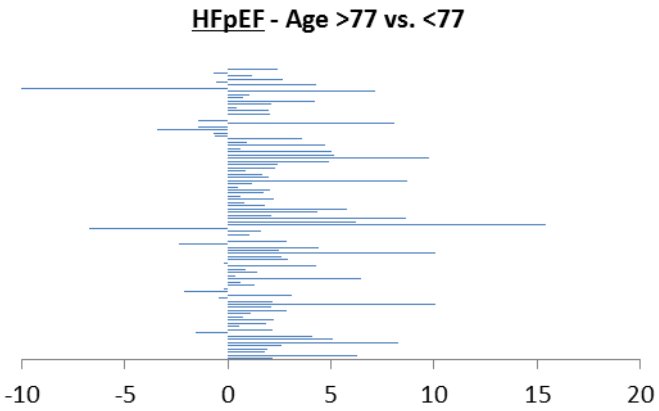
Supplementary files

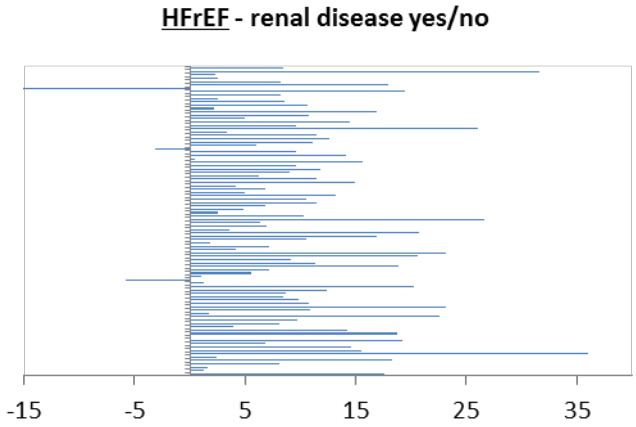
Supplementary Figure 1. Flowchart

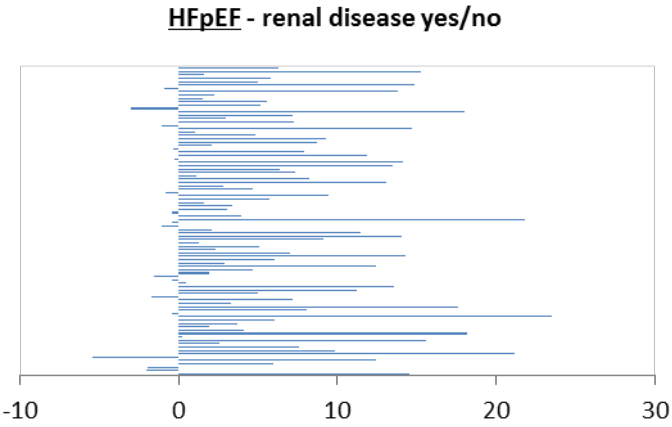


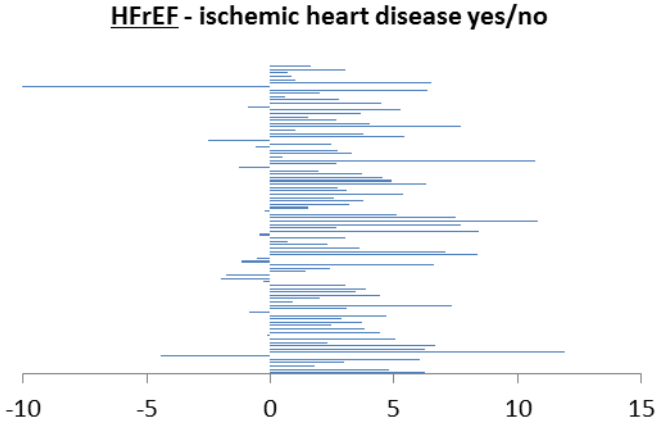
Supplementary Figure 2. Visualizing three falsification hypotheses for age, renal disease and ischemic heart disease in HFrEF and HFpEF

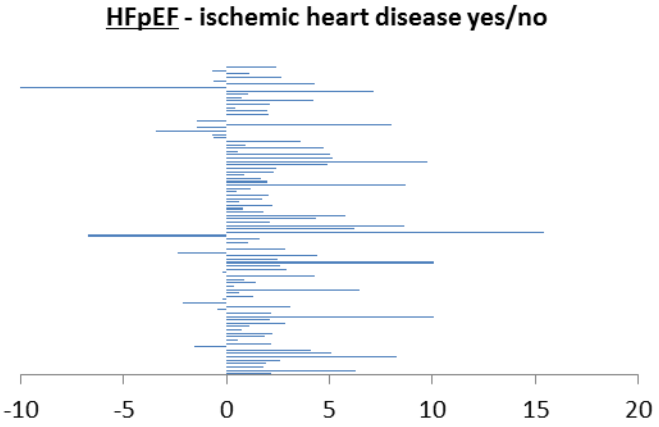












Supplementary Table 1. List of 92 biomarkers OLINK, CVD III panel

ALCAM = CD166 antigen (Other; tumor marker)
APN = Aminopeptidase N (Angiogenesis)
AXL = Tyrosine-protein kinase receptor UFO (Inflammation, immune system, cardiomyocyte injury, angiogenesis)
AZU1 = Azurocidin-1 (Inflammation)
BMLHYDROLASE = Bleomyocin hydrolase (Other / experimental)
BP18 = Interleukin-18 binding protein (Inflammation, immune system)
CASP3 = Caspase-3 (Cell-death/Apoptosis)
CBP1 = Carboxypeptidase B1 (Metabolism)
CCL15 = C-C motif chemokine 15 (Inflammation)
CCL16 = C-C motif chemokine 16 (Inflammation)
CCL22 = C-C motif chemokine 22 (Inflammation)
CCL24 = C-C motif chemokine 24 (Inflammation)
CD163 = Scavenger receptor cysteine-rich type 1 protein m130 (Oxidative stress, inflammation, immune system)
CD93 = Complement component C1q receptor (Atherosclerosis)
CDH5 = Cadherin-5 (Other/Ion-channel (calcium))
CHI3L1 = Chitinase-3-like protein 1 (Inflammation, immune system)
CHIT1 = Chitotriosidase-1 (Atherosclerosis)
CNTN1 = Contactin-1 (Other; tumor marker)
COL1A1 = Collagen alpha-1 (I) chain (Remodeling)
CPA1 = Carboxypeptidase A1 (Metabolism)
CSTB = Cystatin-B (Inflammation, immune system)
CTSD = Cathepsin D (Oxidative stress)
CTSZ = Cathepsin Z (Other; tumor marker)
CXCL16 = C-X-C motif chemokine 16 (Inflammation, other; renal damage)
DLK1 = Protein delta homolog 1 (Other; growth factor)
EGFR2 = Epidermal growth factor receptor (Angiogenesis, inflammation)
EPCAM = Epithelial cell adhesion molecule (Other; tumor marker)
EPHB4 = Ephrin type-B receptor 4 (Angiogenesis)
FABP4 = Fatty acid-binding protein, adipocyte (Inflammation, atherosclerosis)
FAS = Tumor necrosis factor receptor superfamily member 6 (Inflammation, immune system, apoptosis)
GAL3 = Galectin-3 (Remodeling; fibrotic marker)
GAL4 = Galectin-4 (Remodeling)
GDF15 = Growth/differentiation factor 15 (Inflammation)
GRN = Granulins (Inflammation, remodeling)
ICAM2 = Intercellular adhesion molecule 2 (Inflammation, immune system)
IGFBP1 = Insulin-like growth factor-binding protein 1 (Remodeling, inflammation, metabolic marker)
IGFBP2 = Insulin-like growth factor-binding protein 2 (Remodeling)
IGFBP7 = Insulin-like growth factor-binding protein 7 (Remodeling)
IL17RA = Interleukin-17 receptor A (Inflammation, immune system)
IL1RT1 = Interleukin-1 receptor type 1 (Inflammation, immune system)
IL1RT2 = Interleukin-1 receptor type 2 (Inflammation, immune system)
IL2RA = Interleukin-2 receptor subunit Alpha (Inflammation, immune system)
IL6RA = Interleukin-6 receptor subunit Alpha (Inflammation, immune system)
ITGB2 = Integrin beta-2 (Remodeling, angiogenesis)
JAMA = Junctional adhesion molecule A (Inflammation, immune system)
KLK6 = Kallikrein-6 (Inflammation, immune system)
LDLR = Low-density lipoprotein receptor (Artherosclerosis)
LTBR = Lympotoxin-beta receptor (Inflammation, immune system, Artherosclerosis)
MB = Myoglobin (Cardiomyocyte stretch/injury)
MCP1 = Monocyte chemotactic protein 1 (Inflammation, immune system/atherosclerosis)
MEPE = Matrix extracellular phosphoglycoprotein (Other; electrolyte balance)
MMP2 = Matrix metalloproteinase-2 (Remodeling)
MMP3 = Matrix metalloproteinase-3 (Remodeling/angiogenesis)
MMP9 = Matrix metalloproteinase-9 (Remodeling/angiogenesis)
MPO = Myeloperoxidase (Inflammation, immune system)
NOTCH3 = Neurogenic locus notch homolog protein 3 (Remodeling)

NTPROBNP = N-terminal prohormone of brain-type natriuretic peptide (Cardiomyocyte stretch/injury)
OPG = Osteoprotegerin (Inflammation, immune system)
OPN = Osteopontin (Inflammation, immune system, atherosclerosis, fibrosis)
PAI = Plasminogen activator inhibitor 1 (Angiogenesis, other; thrombosis)
PCSK9 = Proprotein convertase subtillisin/kexin type 9 (Metabolic marker)
PDGFSUBUNITA = Platelet-derived growth factor subunit A (Other; growth factor/developmental protein)
PECAM1 = Platelet endothelial cell adhesion molecule (Angiogenesis, endothelial function)
PGLYRP1 = Peptidoglycan recognition protein 1 (Inflammation, immune system)
PI3 = Elafin (Inflammation, immune system)
PLC = Perlecan (Angiogenesis)
PON3 = Paraoxonase (Atherosclerosis, metabolic marker)
PRTN3 = Myeloblastin (Inflammation, immune system)
PSPD = Pulmonary surfactant-associated protein D (Inflammation, immune system)
RARRES2 = Retinoic acid receptor responder protein 2 (Metabolic marker and inflammation, immune system)
RETN = Resistin (Metabolic marker)
SCGB3A2 = Secretoglobin family 3A member 2 (Remodeling, fibrosis)
SELE = E-selectin (Endothelial function)
SELP = P-selectin (Inflammation, immune system)
SHPS1 = Tyrosine-protein phosphatase non-receptor type substrate 1 (Endothelial function, inflammation, immune system)
SPON1 = Spondin-1 (Angiogenesis)
ST2 = ST-2 protein (Remodeling, inflammation, immune system, oxidative stress, cardiomyocyte stretch/injury, angiogenesis)
TFF3 = Trefoil factor 3 (Inflammation, immune system)
TFPI = Tissue factor pathway inhibitor (Haematological marker)
TIMP4 = Metalloproteinase inhibitor 4 (Remodeling/angiogenesis)
TLT2 = Trem-like transcript 2 protein (Inflammation, immune system)
TNFR1 = Tumor necrosis factor receptor 1 (Inflammation, immune system, apoptosis, endothelial function)
TNFR2 = Tumor necrosis factor receptor 2 (Apoptosis, inflammation, immune system)
TNFRSF14 = Tumor necrosis factor receptor superfamily member 14 (Inflammation, immune system, apoptosis)
TNFSF13B = Tumor necrosis factor ligand superfamily member 13B (Inflammation, immune system)
TNRSF10C = Tumor necrosis factor receptor superfamily member 10C (Apoptosis, inflammation, immune system)
TPA = Tissue-type plasminogen activator (Haematological marker)
TR = Transferrin receptor protein 1 (Haematological marker)
TRAP = Tartrate-resistant acid phosphatase type 5 (Inflammation, immune system)
UPA = Urokinase plasminogen activator (Hemostasis, angiogenesis, fibrosis/remodeling, immune system, inflammation)
UPAR = Urokinase plasminogen activator surface receptor (Hemostasis, angiogenesis, fibrosis/remodeling, immune system, inflammation)
VWF = von Willebrand factor (Hemostasis, endothelial dysfunction)

Supplementary Table 2. Median levels (Q1, Q3) of the 92 biomarkers for sinus rhythm and atrial fibrillation in HFrEF

Biomarker	Log2 median level SR	Q1	Q3	Log2 median level AF	Q1	Q3	% Difference AF-SR	P-value
ALCAM	4.28	3.85	4.65	4.37	3.9	4.73	2.1	0.012
APN	4.32	3.9	4.75	4.53	4.09	4.95	4.9	<0.001
AXL	7.22	6.76	7.61	7.34	6.87	7.75	1.7	0.003
AZU1	1.87	1.46	2.4	2.04	1.47	2.57	9.1	<0.001
BMLHYDROLASE	4.57	4.17	4.94	4.68	4.25	5.06	2.4	0.003
BP18	5.8	5.28	6.31	5.85	5.38	6.38	0.9	0.104
CASP3	6.54	5.73	7.72	6.5	5.63	7.6	-0.6	0.299
CBP1	3.47	2.85	4.12	3.62	2.98	4.3	4.3	<0.001
CCL15	6.63	6.14	7.15	6.69	6.22	7.27	0.9	0.044
CCL16	5.54	4.97	6.02	5.67	5.17	6.22	2.3	<0.001
CCL22	1.67	1.11	2.3	1.54	1.06	2.16	-7.8	0.068
CCL24	4.92	4.25	5.62	4.99	4.3	5.71	1.4	0.186
CD163	6.93	6.4	7.4	7	6.53	7.5	1	0.010
CD93	9.05	8.58	9.42	9.07	8.64	9.49	0.2	0.145
CDH5	2.92	2.42	3.39	3.02	2.51	3.47	3.4	0.012
CHI3L1	5.62	4.77	6.54	5.84	5.09	6.59	3.9	0.003
CHIT1	2.44	1.69	3.22	2.5	1.7	3.19	2.5	0.591
CNTN1	2.04	1.58	2.44	2.12	1.63	2.52	3.9	0.010
COL1A1	1.71	1.26	2.16	1.82	1.32	2.21	6.4	0.006
CPA1	3.83	3.19	4.51	4	3.33	4.69	4.4	<0.001
CSTB	4.56	3.9	5.14	4.74	4.18	5.41	3.9	<0.001
CTSD	3.25	2.8	3.71	3.34	2.9	3.8	2.8	0.015
CTSZ	4.34	3.86	4.78	4.34	3.86	4.78	0	0.836
CXCL16	5.68	5.23	6.08	5.72	5.29	6.14	0.7	0.158
DLK1	4.32	3.72	4.99	4.39	3.71	5.02	1.6	0.346
EGFR2	0.74	0.4	1.07	0.79	0.45	1.07	6.8	0.552
EPCAM	3.09	2.42	3.85	2.91	2.26	3.64	-5.8	0.003
EPHB4	1.58	1.21	1.99	1.62	1.3	2.05	2.5	0.121
FABP4	5.21	4.34	6.14	5.53	4.75	6.41	6.1	<0.001
FAS	4.28	3.84	4.72	4.32	3.91	4.79	0.9	0.158
GAL3	4.64	4.14	5.05	4.66	4.17	5.04	0.4	0.707
GAL4	3.12	2.59	3.65	3.19	2.61	3.72	2.2	0.282
GDF15	4.9	4.24	5.6	5.14	4.5	5.9	4.9	0.003
GRN	3.14	2.75	3.49	3.23	2.82	3.58	2.9	0.003
ICAM2	4.44	3.98	4.92	4.56	4.03	5.01	2.7	0.019
IGFBP1	4.52	3.48	5.47	4.92	3.96	5.77	8.8	<0.001
IGFBP2	7.68	7.02	8.3	7.91	7.3	8.49	3	<0.001
IGFBP7	3.7	3.17	4.21	4.07	3.49	4.61	10	<0.001
IL_17RA	3.39	2.89	3.82	3.49	3.01	3.88	2.9	0.043
IL1RT1	5.99	5.54	6.41	6.1	5.63	6.54	1.8	<0.001

IL1RT2	4.16	3.73	4.57	4.23	3.86	4.64	1.7	0.004
IL2RA	3.77	3.24	4.29	3.76	3.22	4.29	-0.3	0.768
IL6RA	10.24	9.82	10.66	10.2	9.84	10.63	-0.4	0.948
ITGB2	4.43	4.04	4.84	4.48	4.05	4.87	1.1	0.156
JAMA	4.48	3.95	5.22	4.62	4	5.22	3.1	0.209
KLK6	2.75	2.37	3.21	2.79	2.37	3.25	1.5	0.582
LDLR	3.27	2.74	3.85	3.04	2.49	3.6	-7	<0.001
LTBR	3.05	2.61	3.56	3.15	2.71	3.69	3.3	0.004
MB	6.22	5.64	6.92	6.42	5.78	7.1	3.2	<0.001
MCP1	2.38	1.96	2.79	2.47	2.04	2.89	3.8	0.004
MEPE	2.37	1.87	2.89	2.42	1.92	2.91	2.1	0.276
MMP2	2.87	2.34	3.43	3.19	2.62	3.66	11.1	<0.001
MMP3	6.85	6.24	7.51	7.06	6.42	7.67	3.1	<0.001
MMP9	3.24	2.59	3.96	3.44	2.68	4.07	6.2	0.006
MPO	3.65	3.22	4.06	3.73	3.27	4.1	2.2	0.101
NOTCH3	3.23	2.75	3.69	3.61	3.1	4.06	11.8	<0.001
NTPROBNP	2.82	1.81	3.91	3.3	2.49	4.19	17	<0.001
OPG	2.73	2.3	3.19	2.85	2.39	3.3	4.4	<0.001
OPN	4.89	4.29	5.49	5.11	4.55	5.72	4.5	<0.001
PAI	4.9	4.04	5.73	4.99	4.16	5.81	1.8	0.114
PCSK9	1.98	1.59	2.34	1.94	1.57	2.35	-2	0.406
PDGFSUBUNITA	1.6	0.9	2.57	1.6	0.93	2.59	0	0.465
PECAM1	4.27	3.79	4.82	4.4	3.91	4.84	3	0.013
PGLYRP1	6.67	6.14	7.19	6.77	6.28	7.26	1.5	0.018
PI3	3.17	2.6	3.84	3.24	2.66	3.84	2.2	0.348
PLC	6.46	6.02	6.95	6.66	6.21	7.1	3.1	<0.001
PON3	4.59	3.87	5.31	4.47	3.74	5.11	-2.6	0.004
PRTN3	4.04	3.57	4.53	4.13	3.67	4.6	2.2	0.018
PSPD	2.2	1.59	2.79	2.3	1.71	2.86	4.5	0.042
RARRES2	11.15	10.81	11.47	11.1	10.7	11.44	-0.4	0.186
RETN	6.02	5.54	6.51	6.12	5.65	6.63	1.7	0.017
SCGB3A2	2.21	1.6	2.9	2.38	1.71	3.18	7.7	0.003
SELE	1.69	1.14	2.25	1.78	1.2	2.26	5.3	0.109
SELP	8.28	7.69	8.86	8.23	7.65	8.83	-0.6	0.367
SHPS1	3.05	2.57	3.52	3.15	2.63	3.59	3.3	0.025
SPON1	1.68	1.29	2.08	1.91	1.42	2.41	13.7	<0.001
ST2	3.65	3.08	4.37	4.03	3.45	4.79	10.4	<0.001
TFF3	5.22	4.67	5.86	5.36	4.87	6	2.7	<0.001
TFPI	7.89	7.45	8.26	7.86	7.39	8.22	-0.4	0.178
TIMP4	4.52	4	5.02	4.68	4.18	5.21	3.5	<0.001
TLT2	3.68	3.2	4.11	3.65	3.13	4.12	-0.8	0.711
TNFR1	4.87	4.33	5.45	5.03	4.44	5.58	3.3	0.003
TNFR2	4.41	3.87	4.96	4.49	3.95	5.07	1.8	0.025
TNFRSF14	4.26	3.76	4.74	4.3	3.82	4.84	0.9	0.114
TNFSF13B	5.52	5.02	5.99	5.6	5.05	6.09	1.4	0.042

TNRSF10C	5.43	4.92	5.91	5.46	4.92	5.99	0.6	0.245
TPA	4.8	4.13	5.66	5.06	4.31	5.92	5.4	<0.001
TR	4.92	4.42	5.48	5.13	4.53	5.65	4.3	<0.001
TRAP	4.61	4.14	5.07	4.4	3.93	4.87	-4.6	<0.001
UPA	4.03	3.6	4.41	4.13	3.69	4.49	2.5	0.005
UPAR	4.13	3.66	4.61	4.27	3.84	4.8	3.4	<0.001
VWF	5.85	5.17	6.84	6.04	5.29	6.87	3.2	0.048

Supplementary Table 3. Median levels (Q1, Q3) of the 92 biomarkers for sinus rhythm and atrial fibrillation in HFpEF

Biomarker	Log2 median level SR	Q1	Q3	Log2 median level AF	Q1	Q3	% Difference AF-SR	p-value
ALCAM	4.62	4.26	4.89	4.62	4.16	4.93	0	0.969
APN	4.55	4.16	4.83	4.6	4.17	5.02	1.1	0.466
AXL	7.57	7.19	7.92	7.53	7.09	7.98	-0.5	0.911
AZU1	2.03	1.67	2.41	2.01	1.52	2.48	-1	0.771
BMLHYDROLASE	4.7	4.34	4.99	4.66	4.36	5.04	-0.9	0.921
BP18	6.36	5.95	6.79	6.29	5.78	6.76	-1.1	0.323
CASP3	6.25	5.57	6.97	6.28	5.43	7.13	0.5	0.969
CBP1	3.58	3.04	4.27	3.74	3.11	4.37	4.5	0.559
CCL15	6.96	6.5	7.44	6.92	6.45	7.46	-0.6	0.911
CCL16	5.85	5.44	6.35	5.82	5.19	6.22	-0.5	0.111
CCL22	1.9	1.4	2.45	1.91	1.23	2.39	0.5	0.617
CCL24	5.33	4.46	6.08	5.01	4.45	5.84	-6	0.235
CD163	7.34	6.88	7.69	7.39	6.87	7.82	0.7	0.630
CD93	9.33	8.95	9.62	9.32	8.84	9.68	-0.1	0.713
CDH5	3.27	2.86	3.63	3.29	2.72	3.7	0.6	0.911
CHI3L1	6.36	5.48	7.18	6.4	5.56	7.27	0.6	0.916
CHIT1	2.84	2.09	3.56	2.66	2.04	3.59	-6.3	0.697
CNTN1	2.37	1.86	2.71	2.34	1.89	2.75	-1.3	0.969
COL1A1	2.03	1.63	2.43	2.1	1.47	2.52	3.4	0.759
CPA1	4.13	3.48	4.76	4.19	3.48	4.8	1.5	0.882
CSTB	5.04	4.43	5.71	4.97	4.41	5.67	-1.4	0.921
CTSD	3.54	3.15	3.93	3.51	3.07	3.91	-0.8	0.709
CTSZ	4.8	4.4	5.17	4.66	4.21	5.1	-2.9	0.110
CXCL16	6.09	5.69	6.43	5.97	5.62	6.35	-2	0.081
DLK1	4.98	4.43	5.57	4.72	4.16	5.31	-5.2	0.039
EGFR2	0.92	0.68	1.18	0.86	0.49	1.14	-6.5	0.111
EPCAM	3.42	2.77	4.15	3.24	2.55	3.78	-5.3	0.040
EPHB4	2.04	1.69	2.41	1.97	1.6	2.37	-3.4	0.279
FABP4	5.93	5.13	6.74	5.94	5.23	6.78	0.2	0.882
FAS	4.72	4.32	5.08	4.61	4.18	4.97	-2.3	0.127
GAL3	5.05	4.61	5.38	4.9	4.39	5.23	-3	0.038
GAL4	3.41	2.92	3.96	3.34	2.83	3.85	-2.1	0.260
GDF15	5.42	4.76	6.03	5.55	4.98	6.08	2.4	0.248
GRN	3.42	3.13	3.74	3.36	3.04	3.76	-1.8	0.818
ICAM2	4.86	4.43	5.24	4.91	4.35	5.3	1	0.696
IGFBP1	4.52	3.54	5.5	4.99	3.91	5.93	10.4	0.012
IGFBP2	8.14	7.47	8.72	8.25	7.71	8.79	1.4	0.235
IGFBP7	4	3.54	4.37	4.28	3.69	4.75	7	0.047
IL_17RA	3.65	3.19	4.07	3.66	3.15	4.04	0.3	0.971
IL1RT1	6.36	5.94	6.71	6.32	5.91	6.78	-0.6	0.969

IL1RT2	4.41	4.06	4.82	4.36	4.05	4.77	-1.1	0.713
IL2RA	4.27	3.8	4.78	4.18	3.68	4.74	-2.1	0.502
IL6RA	10.58	10.18	10.99	10.45	10.01	10.82	-1.2	0.038
ITGB2	4.58	4.16	4.94	4.49	4.1	4.86	-2	0.544
JAMA	4.57	4.11	5.01	4.55	4.06	5.22	-0.4	0.800
KLK6	3.14	2.57	3.54	2.96	2.52	3.44	-5.7	0.114
LDLR	3.67	3.09	4.15	3.16	2.56	3.76	-13.9	<0.001
LTBR	3.63	3.2	4.08	3.57	3.07	4.1	-1.7	0.744
MB	6.85	6.29	7.54	6.78	6.19	7.39	-1	0.552
MCP1	2.73	2.37	3.02	2.7	2.31	3.03	-1.1	0.552
MEPE	2.74	2.32	3.22	2.58	2.06	3.13	-5.8	0.082
MMP2	3.12	2.72	3.62	3.28	2.75	3.77	5.1	0.235
MMP3	7.24	6.61	7.9	7.17	6.55	7.68	-1	0.544
MMP9	3.32	2.61	4.06	3.19	2.53	3.84	-3.9	0.248
MPO	3.93	3.55	4.27	3.85	3.4	4.28	-2	0.679
NOTCH3	3.63	3.19	4.03	3.84	3.35	4.3	5.8	0.032
NTPROBNP	2.33	1.45	3.44	3.12	2.33	3.85	33.9	<0.001
OPG	3.13	2.7	3.44	3.16	2.7	3.56	1	0.713
OPN	5.4	4.84	5.87	5.47	4.84	5.88	1.3	0.771
PAI	4.52	3.74	5.42	4.62	3.9	5.29	2.2	0.911
PCSK9	2.21	1.8	2.54	2.08	1.67	2.47	-5.9	0.248
PDGFSUBUNITA	1.01	0.59	1.8	1.23	0.78	1.78	21.8	0.111
PECAM1	4.42	4.05	4.7	4.45	4	4.84	0.7	0.466
PGLYRP1	7.07	6.61	7.6	7.07	6.47	7.43	0	0.382
PI3	3.52	2.88	4.29	3.52	2.89	4.17	0	0.780
PLC	6.88	6.5	7.32	6.88	6.48	7.33	0	0.956
PON3	5.02	4.22	5.66	4.64	3.98	5.31	-7.6	<0.001
PRTN3	4.36	3.9	4.85	4.41	3.88	5	1.1	0.771
PSPD	2.37	1.82	3	2.42	1.86	2.92	2.1	0.969
RARRES2	11.41	11.06	11.62	11.24	10.94	11.58	-1.5	0.040
RETN	6.41	5.99	6.95	6.35	5.79	6.95	-0.9	0.456
SCGB3A2	2.69	2.12	3.42	2.77	2.14	3.41	3	0.709
SELE	2.12	1.64	2.61	2.03	1.46	2.58	-4.2	0.679
SELP	8.38	7.87	8.78	8.17	7.72	8.75	-2.5	0.276
SHPS1	3.48	3	3.87	3.43	2.98	3.89	-1.4	0.891
SPON1	2	1.61	2.34	2.19	1.74	2.59	9.5	0.031
ST2	4.12	3.66	4.69	4.41	3.76	5.1	7	0.039
TFF3	5.7	5.22	6.37	5.76	5.23	6.36	1.1	0.911
TFPI	8.03	7.73	8.32	7.86	7.48	8.28	-2.1	0.020
TIMP4	5.01	4.47	5.41	5.08	4.59	5.48	1.4	0.550
TLT2	4.06	3.66	4.53	3.92	3.41	4.4	-3.4	0.038
TNFR1	5.55	5.01	6.1	5.43	4.93	6.03	-2.2	0.696
TNFR2	5.09	4.53	5.53	4.97	4.41	5.6	-2.4	0.552
TNFRSF14	4.75	4.21	5.26	4.63	4.11	5.19	-2.5	0.382
TNFSF13B	5.87	5.45	6.29	5.94	5.36	6.38	1.2	0.709

TNRSF10C	5.99	5.42	6.33	5.85	5.28	6.21	-2.3	0.110
TPA	4.81	4.3	5.66	5.07	4.41	5.89	5.4	0.111
TR	5.18	4.6	5.68	5.26	4.72	5.86	1.5	0.248
TRAP	5.16	4.79	5.5	4.68	4.22	5.17	-9.3	<0.001
UPA	4.26	3.91	4.61	4.33	3.9	4.68	1.6	0.646
UPAR	4.58	4.11	5.07	4.58	4.16	5.11	0	0.808
VWF	5.94	5.4	6.67	6.11	5.54	6.73	2.9	0.334

Supplementary Table 4. List of biomarkers with significant interactions between heart rhythm (AF/SR) and heart failure phenotype (HFrEF/HFpEF); univariable and multivariable linear regression model.

Biomarker	**Model 1***	**Model 2****
AXL	0.052	0.116
BP18	0.032	0.182
CCL16	<0.001	<0.001
CCL24	0.029	0.042
CSTB	0.032	0.133
CTSD	0.057	0.101
CTSZ	0.035	0.199
CXCL16	0.010	0.032
DLK1	0.006	0.065
EGFR2	0.023	0.027
EPHB4	0.008	0.064
FABP4	0.012	0.028
FAS	0.019	0.068
GAL3	0.018	0.081
GAL4	0.070	0.394
GRN	0.055	0.110
IL1RT1	0.063	0.164
IL1RT2	0.054	0.072
IL6RA	0.067	0.170
KLK6	0.004	0.042
LDLR	0.018	0.019
LTBR	0.027	0.138
MB	0.010	0.074
MCP1	0.003	0.011
MEPE	0.002	0.020
MMP2	0.043	0.062
MMP3	0.002	0.015
MMP9	0.011	0.008
NOTCH3	0.038	0.054
OPN	0.022	0.068
PGLYRP1	0.030	0.162
PLC	0.015	0.091
PON3	0.031	0.015
RETN	0.028	0.177
TFF3	0.081	0.295
TFPI	0.075	0.065
TIMP4	0.095	0.174
TLT2	0.008	0.051
TNFR1	0.039	0.246
TNFR2	0.038	0.240
TNFRSF14	0.031	0.215
TNRSF10C	0.022	0.080
TRAP	0.009	0.032
UPAR	0.077	0.241

*Model 1: interaction for heart rhythm and heart failure phenotype tested for the 92 biomarkers

**Model 2: interaction for heart rhythm and heart failure phenotype tested in a multivariable model, including age, sex, CAD, BMI, renal disease and hypertension

Supplementary Table 5. Top 5 biomarkers with largest difference between AF and SR in HFrEF and HFpEF, as prognostic predictors of all-cause mortality

HFrEF						
	Sinus rhythm (n=1419)			Atrial fibrillation (n=733)		
	HR	95% CI	P-value	HR	95% CI	P-value
NT-proBNP	1.51	1.41-1.63	**<0.001**	1.42	1.30-1.57	**<0.001**
ST2	1.71	1.54-1.90	**<0.001**	1.59	1.40-1.81	**<0.001**
SPON1	1.76	1.53-2.02	**<0.001**	1.32	1.10-1.57	**0.003**
MMP2	1.51	1.30-1.75	**<0.001**	1.12	0.94-1.33	0.20
NOTCH3	1.50	1.30-1.73	**<0.001**	1.02	0.85-1.22	0.85
HFpEF						
	Sinus rhythm (n=286)			Atrial fibrillation (n=238)		
	HR	95% CI	P-value	HR	95% CI	P-value
NT-proBNP	1.53	1.37-1.71	**<0.001**	1.52	1.27-1.81	**<0.001**
ST2	1.72	1.42-2.08	**<0.001**	1.58	1.29-1.94	**<0.001**
SPON1	1.76	1.32-2.34	**<0.001**	1.97	1.44-2.69	**<0.001**
IGFBP1	1.54	1.31-1.82	**<0.001**	1.42	1.22-1.66	**<0.001**
PDGFSUBUNITA	1.13	0.92-1.98	0.26	1.04	0.82-1.30	0.76

AF = atrial fibrillation, SR = sinus rhythm, HFrEF = heart failure with reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, HR = hazard ratio, CI = confidence interval, NT-proBNP = = N-terminal pro B-type natriuretic peptide, ST2 = ST-2 protein, SPON1 = Spondin-1, MMP2 = Matrix metalloproteinase-2, NOTCH3 = Neurogenic locus notch homolog protein 3, IGFBP1 = Insulin-like growth factor-binding protein, PDGFSUBUNITA = Platelet-derived growth factor subunit A.